

IN THE CLAIMS

Please amend claims 30 and 31 as shown below. Please add new claims 45-64 as shown below. The following listing of claims replaces all prior listings.

1. (Canceled).
2. (Previously presented) The article of manufacture of claim 30, wherein E₁, E₃, and E₄ are -O, and E₂ is -NH.
3. (Previously presented) The article of manufacture of claim 30, wherein R₁ and R₂ are -H, alkyl, or substituted alkyl, and R₃ is hydroxy or alkoxy.
4. (Previously presented) The article of manufacture of claim 30, wherein R₁ is substituted alkyl.
5. (Previously presented) The article of manufacture of claim 4, wherein the substituted alkyl is a halogenated alkyl.
6. (Previously presented) The article of manufacture of claim 5, wherein the halogenated alkyl is a chlorinated alkyl.
- 7-14. (Canceled)
15. (Withdrawn) The method of claim 27, wherein the mammalian cell is human.
16. (Withdrawn) The method of claim 27, wherein the disorder is characterized by the formation of neoplasms.
17. (Withdrawn) The method of claim 16, wherein the neoplasms are selected from mammary, small-cell lung, non-small-cell lung, colorectal, leukemia, melanoma, pancreatic adenocarcinoma, central nervous system (CNS), ovarian, prostate, sarcoma of soft tissue or bone,

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head and neck, gastric which includes thyroid and non-Hodgkin's disease, stomach, myeloma, bladder, renal, neuroendocrine which includes thyroid and non-Hodgkin's disease and Hodgkin's disease neoplasms.

18. (Withdrawn) The method of claim 17, wherein the neoplasms are colorectal neoplasms.

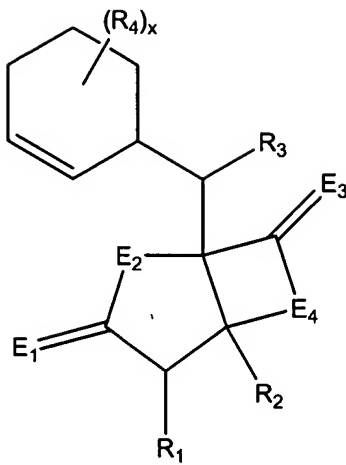
19. (Withdrawn) A method for inhibiting proliferation of mammalian cells, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of claim 23.

20. (Withdrawn) The method of claim 19, wherein the mammalian cells are human.

21. (Withdrawn) The method of claim 20, wherein the cells are selected from mammary, small-cell lung, non-small-cell lung, colorectal, leukemia, melanoma, pancreatic adenocarcinoma, central nervous system (CNS), ovarian, prostate, sarcoma of soft tissue or bone, head and neck, gastric, stomach, myeloma, bladder, renal, and neuroendocrine cells.

22-26. (Canceled)

27. (Withdrawn) A method for treating a mammalian cell proliferative disorder, comprising administering to a subject in need thereof a therapeutically effective amount of a compound having the structure:



I

wherein:

R_1 to R_3 are each independently $-H$, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkyl, substituted cycloalkyl, alkoxy, substituted alkoxy, thioalkyl, substituted thioalkyl, hydroxy, halogen, amino, amido, carboxyl,

$-C(O)H$, acyl, oxyacyl, carbamate, sulfonyl, sulfonamide, or sulfuryl,

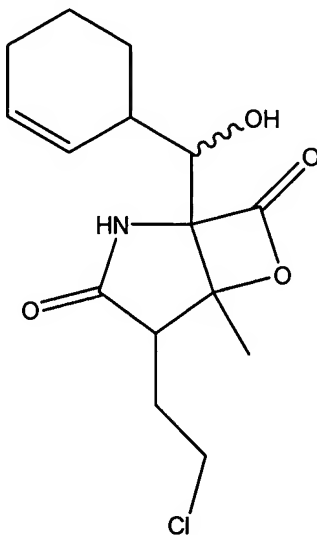
each R_4 is independently alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl,

E_1 to E_4 are each independently $-O$, $-NR_5$, or $-S$, wherein R_5 is $-H$ or C_1-C_6 alkyl, and

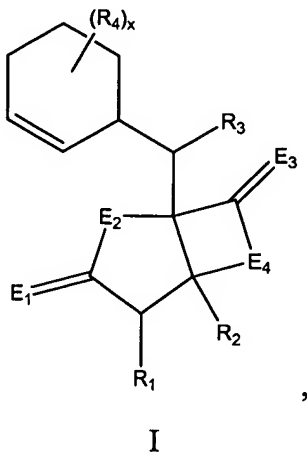
x is 0 to 8'

thereby treating a mammalian cell proliferative disorder.

28. (Withdrawn) The method of claim 27, wherein the compound has the structure:



29. (Withdrawn) A method for producing a compound having the ability to inhibit the proliferation of hyperproliferative mammalian cells, wherein said compound has structure (I):



wherein:

R₁ to R₃ are each independently -H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted

aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkyl, substituted cycloalkyl, alkoxy, substituted alkoxy, thioalkyl, substituted thioalkyl, hydroxy, halogen, amino, amido, carboxyl, -C(O)H, acyl, oxyacyl, carbamate, sulfonyl, sulfonamide, or sulfuryl,

each R_4 is independently alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl,

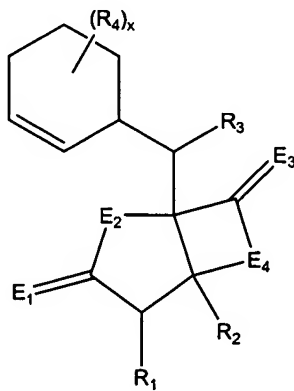
E_1 to E_4 are each independently -O, -NR₅, or -S, wherein R₅ is -H or C₁-C₆ alkyl, and

x is 0 to 8,

the method comprising:

- a) cultivating a culture of a *Salinospora* sp. strain CNB392 or CNB476;
- b) isolating from the culture at least one compound of structure (I).

30. (Currently amended) An article of manufacture comprising packaging material and a pharmaceutical composition contained within said packaging material, wherein said packaging material comprises a label which indicates that said pharmaceutical composition can be used for treatment of a cell proliferative disorders and wherein said pharmaceutical composition comprises at least one compound having the structure (I):



(I)

wherein:

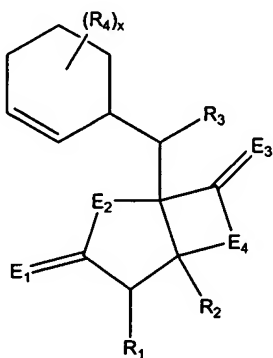
R₁ to R₃ are each independently -H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkyl, substituted cycloalkyl, alkoxy, substituted alkoxy, thioalkyl, substituted thioalkyl, hydroxy, halogen, amino, amido, carboxyl, -C(O)H, acyl, oxyacyl, carbamate, ~~sulfonyl~~, sulfonamide, ~~or~~ sulfuryl, or substituents comprising a sulfonyl moiety,

each R₄ is independently alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl,

E₁ to E₄ are each independently -O, -NR₅, or -S, wherein R₅ is -H or C₁-C₆ alkyl, and

x is 0 to 8.

31. (Currently amended) A pharmaceutical composition ~~useful for inhibiting proliferation of hyperproliferative mammalian cells~~, comprising an effective amount of a compound having the structure (I) and a pharmaceutically acceptable carrier:



I

wherein:

R₁ to R₃ are each independently –H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkyl, substituted cycloalkyl, alkoxy, substituted alkoxy, thioalkyl, substituted thioalkyl, hydroxy, halogen, amino, amido, carboxyl, –C(O)H, acyl, oxyacyl, carbamate, ~~sulfonyl~~, sulfonamide, or sulfuryl, or substituents comprising a sulfonyl moiety,

each R₄ is independently alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl,

E₁ to E₄ are each independently –O, –NR₅, or –S, wherein R₅ is –H or C₁–C₆ alkyl, and

x is 0 to 8,

and further comprising at least one additional anti-neoplastic agent other than the compound having the structure (I).

32. (Previously presented) The composition of claim 31, wherein E₁, E₃, and E₄ are –O, and E₂ is –NH.

33. (Previously presented) The composition of claim 31, wherein R₁ and R₂ are –H, alkyl, or substituted alkyl, and R₃ is hydroxy or alkoxy.

34. (Previously presented) The composition of claim 31, wherein R₁ is substituted alkyl.

35. (Previously presented) The composition of claim 34, wherein the substituted alkyl is a halogenated alkyl.

36. (Previously presented) The composition of claim 35, wherein the halogenated alkyl is a chlorinated alkyl.

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37. (Previously presented) The composition of claim 31, wherein the anti-neoplastic agent comprises an antimetabolite, an alkylating agent, a plant alkaloid, an antibiotic, a hormone, or an enzyme.

38. (Previously presented) The composition of claim 37, wherein the antimetabolite is selected from a group consisting of methotrexate, 5-fluorouracil, 6-mercaptopurine, cytosine arabinoside, hydroxyurea, and 2-chlorodeoxyadenosine.

39. (Previously presented) The composition of claim 37, wherein the alkylating agent is selected from a group consisting of cyclophosphamide, melphalan, busulfan, paraplantin, chlorambucil, and nitrogen mustard.

40. (Previously presented) The composition of claim 37, wherein the plant alkaloid is selected from a group consisting of vincristine, vinblastine, taxol, and etoposide.

41. (Previously presented) The composition of claim 37, wherein the antibiotic is selected from a group consisting of doxorubicin (adriamycin), daunorubicin, mitomycin c, and bleomycin.

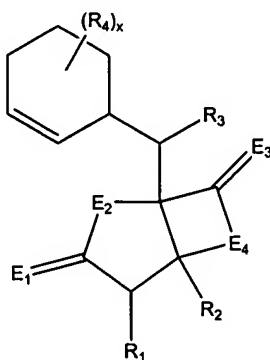
42. (Previously presented) The composition of claim 37, wherein the hormone is selected from a group consisting of calusterone, diomostavolone, propionate, epitiostanol, mepitiothane, testolactone, tamoxifen, polyestradiol phosphate, megestrol acetate, flutamide, nilutamide, and trilotate.

43. (Previously presented) The composition of claim 37, wherein the enzyme is selected from a group consisting of L-asparaginase derivatives and aminoacridine derivatives.

44. (Previously presented) The composition of claim 43, wherein the aminoacridine derivative is amsacrine.

45. (New) An article of manufacture comprising packaging material and a pharmaceutical composition contained within said packaging material, wherein said packaging material

comprises a label which indicates that said pharmaceutical composition can be used for treatment of a cell proliferative disorder and wherein said pharmaceutical composition comprises at least one compound having the structure (I):



(I)

wherein:

R₁ to R₃ are each independently -H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkyl, substituted cycloalkyl, alkoxy, substituted alkoxy, thioalkyl, substituted thioalkyl, hydroxy, halogen, amino, amido, carboxyl, -C(O)H, acyl, oxyacyl, carbamate, sulfonamide, or sulfuryl, or substituents comprising a sulfonyl moiety,

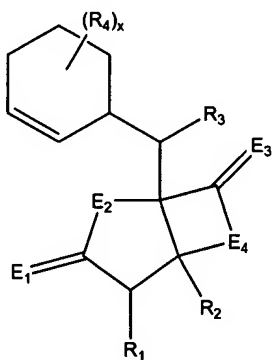
each R₄ is independently alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl,

E₁ to E₄ are each independently -O-, -NR₅, or -S-, wherein R₅ is -H or C₁-C₆ alkyl, and

x is 0 to 8,

wherein the cell proliferative disorder is colon cancer.

46. (New) The article of manufacture of claim 45, wherein E_1 , E_3 , and E_4 are $-O$, and E_2 is $-NH$.
47. (New) The article of manufacture of claim 45, wherein R_1 and R_2 are $-H$, alkyl, or substituted alkyl, and R_3 is hydroxy or alkoxy.
48. (New) The article of manufacture of claim 45, wherein R_1 is substituted alkyl.
49. (New) The article of manufacture of claim 48, wherein the substituted alkyl is a halogenated alkyl.
50. (New) The article of manufacture of claim 49, wherein the halogenated alkyl is a chlorinated alkyl.
51. (New) A pharmaceutical composition, comprising an effective amount of a compound having the structure (I) and a pharmaceutically acceptable carrier:



wherein:

R_1 to R_3 are each independently $-H$, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic,

substituted heterocyclic, cycloalkyl, substituted cycloalkyl, alkoxy, substituted alkoxy, thioalkyl, substituted thioalkyl, hydroxy, halogen, amino, amido, carboxyl, -C(O)H, acyl, oxyacyl, carbamate, sulfonamide, or sulfuryl, or substituents comprising a sulfonyl moiety,

each R₄ is independently alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl,

E₁ to E₄ are each independently -O, -NR₅, or -S, wherein R₅ is -H or C₁-C₆ alkyl, and

x is 0 to 8,

and further comprising at least one additional anti-neoplastic agent,

wherein the composition is useful for treatment of colon cancer.

52. (New) The composition of claim 51, wherein E₁, E₃, and E₄ are -O, and E₂ is -NH.

53. (New) The composition of claim 51, wherein R₁ and R₂ are -H, alkyl, or substituted alkyl, and R₃ is hydroxy or alkoxy.

54. (New) The composition of claim 51, wherein R₁ is substituted alkyl.

55. (New) The composition of claim 54, wherein the substituted alkyl is a halogenated alkyl.

56. (New) The composition of claim 55, wherein the halogenated alkyl is a chlorinated alkyl.

57. (New) The composition of claim 51, wherein the anti-neoplastic agent comprises an antimetabolite, an alkylating agent, a plant alkaloid, an antibiotic, a hormone, or an enzyme.

58. (New) The composition of claim 57, wherein the antimetabolite is selected from a group consisting of methotrexate, 5-fluorouracil, 6-mercaptopurine, cytosine arabinoside, hydroxyurea, and 2-chlorodeoxyadenosine.

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59. (New) The composition of claim 57, wherein the alkylating agent is selected from a group consisting of cyclophosphamide, melphalan, busulfan, paraplantin, chlorambucil, and nitrogen mustard.

60. (New) The composition of claim 57, wherein the plant alkaloid is selected from a group consisting of vincristine, vinblastine, taxol, and etoposide.

61. (New) The composition of claim 57, wherein the antibiotic is selected from a group consisting of doxorubicin (adriamycin), daunorubicin, mitomycin c, and bleomycin.

62. (New) The composition of claim 57, wherein the hormone is selected from a group consisting of calusterone, diomostavolone, propionate, epitiostanol, mepitiothane, testolactone, tamoxifen, polyestradiol phosphate, megestrol acetate, flutamide, nilutamide, and trilotane.

63. (New) The composition of claim 57, wherein the enzyme is selected from a group consisting of L-asparaginase derivatives and aminoacridine derivatives.

64. (New) The composition of claim 63, wherein the aminoacridine derivative is amsacrine.